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EP 00/07358

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

99870170.0

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See for title page 1 of the description

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NON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

- 5 The present invention concerns IL-5 inhibiting 6-azauracil derivatives useful for treating eosinophil-dependent inflammatory diseases; to processes for their preparation and compositions comprising them. It further relates to their use as a medicine.

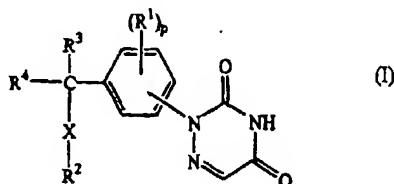
10 Eosinophil influx, leading to subsequent tissue damage, is an important pathogenic event in bronchial asthma and allergic diseases. The cytokine interleukin-5 (IL-5), produced mainly by T lymphocytes as a glycoprotein, induces the differentiation of eosinophils in bone marrow and, primes eosinophils for activation in peripheral blood and sustains their survival in tissues. As such, IL-5 plays a critical role in the process of eosinophilic inflammation. Hence, the possibility that inhibitors of IL-5 production would reduce the
15 production, activation and/or survival of eosinophils provides a therapeutic approach to the treatment of bronchial asthma and allergic diseases such as, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and also other eosinophil-dependent inflammatory diseases.

- 20 Steroids, which strongly inhibit IL-5 production *in vitro*, have long been used as the only drugs with remarkable efficacy for bronchial asthma and atopic dermatitis, but they cause various serious adverse reactions such as diabetes, hypertension and cataracts. Therefore, it would be desirable to find non-steroidal compounds having the ability to inhibit IL-5 production in human T-cells and which have little or no adverse
25 reactions.

US 4,631,278 discloses α -aryl-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)-benzeneacetonitriles and US 4,767,760 discloses 2-(substituted phenyl)-1,2,4-triazine-3,5(2H,4H)-diones, all having anti-protozoal activity, in particular, anti-coccidial
30 activity. EP 831,088 discloses 1,2,4-triazine-3,5-diones as anticoccidial agents. WO99/02505 discloses 6-azauracil derivatives which prove to be potent inhibitors of the production of IL-5.

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The present invention is concerned with the compounds of formula

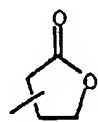


the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein :

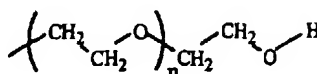
- 5 p represents an integer being 0, 1, 2, 3 or 4;
- X represents O, S, NR^5 or a direct bond or $-X-R^2$ taken together may represent cyano;
- Y represents O, S, NR^5 , or $S(O)_2$;
- each R^1 independently represents $C(=O)-Z-R^{14}$, C_{1-6} alkyl, halo, polyhalo C_{1-6} alkyl, hydroxy, mercapto, C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkylcarbonyloxy, aryl, cyano,
- 10 nitro, Het^3 , R^6 , NR^7R^8 or C_{1-4} alkyl substituted with $C(=O)-Z-R^{14}$, Het^3 , R^6 or NR^7R^8 ;
- R^2 represents Het^1 , C_{3-7} cycloalkyl optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkyl or C_{1-6} alkyl substituted with one or two substituents selected from $C(=O)-Z-R^{14}$, hydroxy, cyano, amino, mono- or di(C_{1-4} alkyl)amino, C_{1-6} alkyloxy optionally substituted with $C(=O)-Z-R^{14}$, C_{1-6} alkylsulfonyloxy, C_{3-7} cycloalkyl optionally
- 15 substituted with $C(=O)-Z-R^{14}$, aryl, aryloxy, arylthio, Het^1 , Het^1 oxy and Het^1 thio; and if X is O, S or NR^5 , then R^2 may also represent aminothiocarbonyl, C_{1-4} alkylcarbonyl optionally substituted with $C(=O)-Z-R^{14}$, C_{1-4} alkylthiocarbonyl optionally substituted with $C(=O)-Z-R^{14}$, arylcarbonyl, arylthiocarbonyl, Het^1 carbonyl or Het^1 thiocarbonyl;
- R^3 represents hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl;
- 20 R^4 represents hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl; or
- R^3 and R^4 taken together form a C_{2-6} alkanediyl;
- R^5 represents hydrogen or C_{1-4} alkyl;
- each R^6 independently represents C_{1-6} alkylsulfonyl, aminosulfonyl, mono- or di- (C_{1-4} alkyl)aminosulfonyl, mono- or di(benzyl)aminosulfonyl,
- 25 polyhalo C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, phenyl C_{1-4} alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*- C_{1-4} alkyl-*N*-piperidinylaminosulfonyl or mono-or di(C_{1-4} alkyl)amino C_{1-4} alkylsulfonyl;

- each R⁷ and each R⁸ are independently selected from hydrogen, C₁₋₄alkyl, hydroxy-C₁₋₄alkyl, dihydroxyC₁₋₄alkyl, aryl, arylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl,
- 5 Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ and R⁶;
- R⁹ and R¹⁰ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl,
- 10 phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ and R⁶;
- each R¹¹ independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C₁₋₄alkyloxy optionally substituted with C(=O)-Z-R¹⁴, formyl,
- 15 trihaloC₁₋₄alkylsulfonyloxy, R⁶, NR⁷R⁸, C(=O)NR¹⁵R¹⁶, -C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, aryl, aryloxy, arylcarbonyl, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, C₃₋₇cycloalkyloxy optionally substituted with C(=O)-Z-R¹⁴, phthalimide-2-yl, Het³, Het⁴ and C(=O)Het³;
- R¹² and R¹³ are each independently selected from hydrogen, C₁₋₄alkyl, hydroxyC₁₋₄alkyl, dihydroxyC₁₋₄alkyl, phenyl, phenylC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, phenylcarbonyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, phenylaminocarbonyl,
- 20 phenylaminothiocarbonyl, C₃₋₇cycloalkyl, pyridinylC₁₋₄alkyl, C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, -C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴ and R⁶;
- each R¹⁴ independently represents C₁₋₄alkyl substituted with one or more substituents
- 25 selected from phenyl, di-C₁₋₄alkylamino, cyano, Het¹ and C₃₋₇cycloalkyl, hydrogen, C₁₋₂₀acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C₁₋₂₀alkyl, C₃₋₇cycloalkyl, polyhaloC₁₋₂₀alkyl or a radical of formula

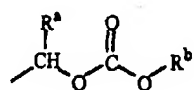
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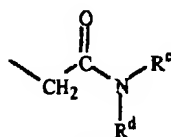
(a)



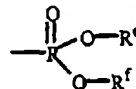
(b)



(c)



(d)

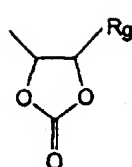


(e)

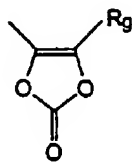
wherein n is 0 to 5;

R^a , R^b , R^c , R^d , R^e and R^f are each independently hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl; or

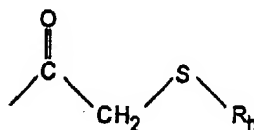
5 R^e and R^f taken together may form $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$; or a radical of formula



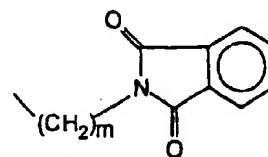
(h)



(i)



(j)



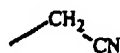
(k)

wherein m is 1 to 4

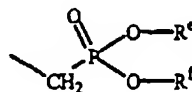
10 R_g and R_h are each independently C_{1-4} alkyl;

each Z independently represents O, S, NH, $-CH_2-O-$ or $-CH_2-S-$ whereby $-CH_2-$ is attached to the carbonyl group;

$-Z-R^{14}$ taken together form a radical of formula



(f)



(g)

15 R^{15} and R^{16} are each independently selected from dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, $-C(=O)-Z-R^{14}$, arylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, pyridinyl C_{1-4} alkyl, Het³ or R^6 ;

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aminocarbonylmethylene or mono- or di(C₁₋₄alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each

independently selected from nitro, azido, cyano, halo, hydroxy, C₁₋₄alkyl, C₃₋₇cyclo-

alkyl, C₁₋₄alkoxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴,

5 R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkoxy, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;

Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazoliny,

pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl,

10 thiolanyl, dioxolanyl, oxazolyl, oxazoliny, isoxazolyl, thiazolyl, thiazolinyl,

isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl,

pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl,

dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl,

isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indoliny, purinyl,

15 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnoliny,

phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl, oxazolopyridinyl and

imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally

be substituted with one, or where possible, two or three substituents each

independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or

20 two substituents independently selected from Het² and R¹¹;

Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazoliny,

pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl,

thiolanyl, dioxolanyl, oxazolyl, oxazoliny, isoxazolyl, thiazolyl, thiazolinyl,

isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl,

25 pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl,

benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl,

indoliny, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl,

isoquinolyl, cinnoliny, phtalazinyl, quinazolinyl, quinoxalinyl, thiazolopyridinyl,

oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each

30 independently may optionally be substituted with one, or where possible, two or three

substituents each independently selected from R¹¹ and C₁₋₄alkyl optionally substituted

with one or two substituents independently selected from R¹¹;

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Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkylcarbonyl, piperidinyl, NR¹²R¹³, C(=O)-Z-R¹⁴, R⁶ and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy, C₁₋₄alkyloxy, phenyl, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴, R⁶ and NR¹²R¹³;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl provided however that

- R² is other than C₁₋₄alkyloxycarbonylC₁₋₄alkyl, aminocarbonyl; and
- R⁷, R⁸, R⁹ and R¹⁰ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl, C₁₋₄alkyloxycarbonylcarbonyl C(=O)-O-R¹⁴, C₁₋₄alkanediylC(=O)-O-R¹⁴ and -Y-C₁₋₄alkanediylC(=O)-O-R¹⁴; and
- R¹² and R¹³ are other than C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl, C₁₋₄alkylcarbonylcarbonyl; and
- R¹¹ is other than C(=O)-O-R¹⁴, Y-C₁₋₄alkanediyl - C(=O)-OR¹⁴, C(=O)NH₂, C(=O)NHC₁₋₄alkyl or C(=O)NHC₃₋₇cycloalkyl; and
- R¹⁴ is other than hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl, aminocarbonylmethylene, mono- or di (C₁₋₄alkyl) aminocarbonylmethylene in the event Z is O; and
- R¹⁵ and R¹⁶ are other than aminocarbonyl, C₁₋₄alkylcarbonyloxy-C₁₋₄alkylcarbonyl, hydroxy C₁₋₄alkylcarbonyl or C₁₋₄alkyloxycarbonylcarbonyl; and
- Aryl is other than phenyl substituted with C(=O)-O-R¹⁴, C(=O)NH₂, C(=O)NHC₁₋₄alkyl, C(=O)NHC₃₋₇cycloalkyl and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁴ or Y-C₁₋₄alkanediyl - C(=O)-O-R¹⁴; and
- Het³ is other than a monocyclic heterocycle substituted with C(=O)-O-R¹⁴ and/or with C₁₋₄alkyl substituted with C(=O)-O-R¹⁴ and/or Y-C₁₋₄alkanediyl - C(=O)-O-R¹⁴; and
- The said compound of formula (I) contains at least one - C(=O)-Z-R¹⁴ moiety.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₃₋₇cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl,

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- cyclohexyl and cycloheptyl; C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl, 2,2-dimethylethyl and the like; C₁₋₆alkyl is meant to include C₁₋₄alkyl and the higher homologues thereof having 5 or
- 5 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like C₁₋₂₀alkyl is meant to include C₁₋₆alkyl and the higher homologues thereof having 7 to 20 carbon atoms such as, for example, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, octadecyl, nonadecyl, eicosyl and the like C₁₋₂₀alkyl is meant to include C₁₋₂₀alkyl except for C₁₋₄alkyl; polyhaloC₁₋₄alkyl is defined
- 10 as polyhalosubstituted C₁₋₄alkyl, in particular C₁₋₄alkyl substituted with 1 to 6 halogen atoms, more in particular difluoro- or trifluoromethyl; polyhaloC₁₋₆alkyl is defined as polyhalosubstituted C₁₋₆alkyl; polyhaloC₁₋₂₀alkyl is defined as polyhalosubstituted C₁₋₂₀alkyl. The term C₁₋₄alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 1 to 4 carbon atoms such as, for
- 15 example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like; C₂₋₆alkanediyl defines bivalent straight or branch chained alkanediyl radicals having from 2 to 6 carbon atoms such as, for example, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like.
- 20 Het¹, Het², Het³ and Het⁴ are meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het¹, Het², Het³ and Het⁴, for instance, pyrrolyl also includes 2*H*-pyrrolyl; triazolyl includes 1,2,4-triazolyl and 1,3,4-triazolyl; oxadiazolyl includes 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and 1,3,4-oxadiazolyl; thiadiazolyl includes 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,
- 25 1,2,5-thiadiazolyl and 1,3,4-thiadiazolyl; pyranyl includes 2*H*-pyranyl and 4*H*-pyranyl.

The heterocycles represented by Het¹, Het², Het³ and Het⁴ may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate. Thus, for example, when the heterocycle is imidazolyl, it may be a

30 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and 5-imidazolyl; when it is thiazolyl, it may be 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; when it is triazolyl, it may be 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl, 1,3,4-triazol-1-yl and 1,3,4-triazol-2-yl; when it

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is benzthiazolyl, it may be 2-benzthiazolyl, 4-benzthiazolyl, 5-benzthiazolyl, 6-benzthiazolyl and 7-benzthiazolyl.

The C₁₋₂₀ acyl is derived from

5	acetic acid	CH ₃ COOH	tridecanoic acid	C ₁₂ H ₂₃ COOH
	propionic acid	C ₂ H ₅ COOH	myristic acid	C ₁₃ H ₂₇ COOH
	butyric acid	C ₃ H ₇ COOH	pentadecanoic acid	C ₁₄ H ₂₉ COOH
	valeric acid	C ₄ H ₉ COOH	palmitic acid	C ₁₅ H ₃₁ COOH
	hexanoic acid	C ₅ H ₁₁ COOH	heptadecanoic acid	C ₁₆ H ₃₃ COOH
10	heptanoic acid	C ₆ H ₁₃ COOH	stearic acid	C ₁₇ H ₃₅ COOH
	octanoic acid	C ₇ H ₁₅ COOH	oleic acid	C ₁₇ H ₃₃ COOH
	nonanoic acid	C ₈ H ₁₇ COOH	linolic acid	C ₁₇ H ₃₁ COOH
	decanoic acid	C ₉ H ₁₉ COOH	linolenic acid	C ₁₇ H ₂₉ COOH
	undecanoic acid	C ₁₀ H ₂₁ COOH	nonadecanoic acid	C ₁₈ H ₃₇ COOH
15	lauric acid	C ₁₁ H ₂₃ COOH	icosanoic acid	C ₁₉ H ₃₉ COOH

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to
 30 comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-
 35 acetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzene-sulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by
 40 treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for
 45 example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium,

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sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

10 The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide. For example, one or more nitrogen atoms of any of the heterocycles in the definition of Het¹, Het² and Het³ may be *N*-oxidized.

15 Some of the compounds of formula (I) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention. For example, a hydroxy substituted triazine moiety may also exist as the corresponding triazinone moiety; a hydroxy substituted pyrimidine moiety may also exist as the corresponding pyrimidinone moiety.

20

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms in which the compounds of formula (I) can exist. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. More in particular, stereogenic centers may have the *R*- or *S*-configuration, used herein in accordance with Chemical Abstracts nomenclature. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

25 The compounds of formula (I) and some of the intermediates in the present invention contain one or more asymmetric carbon atoms. The pure and mixed stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their pharmaceutically acceptable addition salts, and their stereochemically isomeric forms.

5

An interesting group of compounds are those compounds of formula (I) wherein the 6-azauracil moiety is connected to the phenyl ring in the para or meta position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents; preferably in the para position.

10

Another interesting group contains those compounds of formula (I) wherein one or more of the following restrictions apply :

- p is 0, 1 or 2;
- X is S, NR⁵, or a direct bond; more in particular NH or a direct bond;
- 15 • each R¹ independently is halo, polyhaloC₁₋₄alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy or aryl, preferably, chloro or trifluoromethyl, more preferably chloro;
- R² is Het¹ or C₁₋₆alkyl substituted with one or two substituents selected from hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C(=O)-Z-R¹⁴, C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl
- 20 • optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if X is O, S or NR⁵, then R² may also represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; particularly R² is Het¹ or in the event X is NH, R²
- 25 • may also be aminothiocarbonyl or Het¹carbonyl;
- R³ is hydrogen, methyl, ethyl, propyl or cyclohexyl; preferably, methyl;
- R⁴ is hydrogen or methyl; preferably, methyl;
- R³ and R⁴ are taken together to form a 1,4-butanediyl;
- R⁶ is C₁₋₆alkylsulfonyl or aminosulfonyl;
- 30 • R⁷ and R⁸ are each independently hydrogen, C₁₋₄alkyl, Het³ or R⁶;
- R⁹ and R¹⁰ are each independently hydrogen, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkylcarbonyl, aminocarbonyl, Het³carbonyl, Het³ or R⁶;

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- R¹¹ is cyano, nitro halo, C₁₋₄alkyloxy, formyl, NR⁷R⁸, C(=O)NR¹⁵R¹⁶, -C(=O)-Z-R¹⁴, aryl, arylcarbonyl, Het³, Het⁴ and C(=O)Het³;
- R¹⁴ is dihydrofuranyl, C₁₋₂₀alkyl, C₁₋₄alkyl substituted with one or more substituents selected from phenyl, C₁₋₄alkylamino, cyano, Het¹ and C₂₋₇cycloalkyl;
- 5 • aryl is phenyl optionally substituted with one, two or three substituents each independently selected from nitro, cyano, halo, hydroxy, C₁₋₄alkyl, C₂₋₇cycloalkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-O-R¹⁴, -O-R⁶, phenyl, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, Het³
10 or NR⁹R¹⁰;
- Het¹ is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl,
15 wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
preferably Het¹ is imidazolyl, oxadiazolyl, thiazolyl or pyridinyl each independently and optionally substituted with one, or where possible, two or three substituents
20 each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹;
- Het² is an aromatic heterocycle; more in particular furanyl, thienyl, pyridinyl or benzothienyl, wherein said aromatic heterocycles each independently may
25 optionally be substituted with one, or where possible, two or three substituents each independently selected from R¹¹ and C₁₋₄alkyl;
- Het³ is piperidinyl, piperazinyl, morpholinyl and tetrahydropyranyl each independently and optionally substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl, C₁₋₄alkylcarbonyl, piperidinyl and C₁₋₄alkyl substituted with one or two substituents independently selected from hydroxy,
30 C₁₋₄alkyloxy and phenyl;
- Het⁴ is thienyl.

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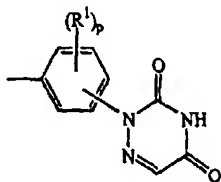
Special compounds are those compounds of formula (I) wherein p is 2 and both R¹ substituents are chloro; more preferably the two chloro substituents are in the ortho positions relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

- 5 Particular compounds are those compounds of formula (I) wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.
- 10 Other particular compounds are those compounds of formula (I) wherein X is a direct bond and R² is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, in particular imidazolyl, oxadiazolyl, thiazolyl, pyrimidinyl or pyridinyl,
- 15 wherein said monocyclic heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹; more in particular R² is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.
- 20 Preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are both methyl and -X-R² is Het¹ wherein Het¹ suitably is optionally substituted thiazolyl, pyridinyl or oxadiazolyl.

- More preferred compounds are those compounds of formula (I) wherein R³ and R⁴ are
- 25 both methyl, -X-R² is optionally substituted 2-thiazolyl or 3-oxadiazolyl, the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents, and p is 2 whereby both R¹ substituents are chloro positioned ortho relative to the carbon atom bearing the -X-R², R³ and R⁴ substituents.

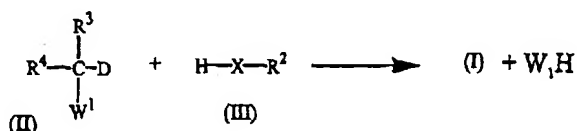
- 30 In order to simplify the structural representation of the compounds of formula (I), the group

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will hereinafter be represented by the symbol D.

- Compounds of formula (I) can generally be prepared by reacting an intermediate of
 5 formula (II) wherein W¹ is a suitable leaving group such as, for example, a halogen
 atom, with an appropriate reagent of formula (III).



- Said reaction may be performed in a reaction-inert solvent such as, for example,
 acetonitrile, *N,N*-dimethylformamide, acetic acid, tetrahydrofuran, ethanol or a mixture
 10 thereof. Alternatively, in case the reagent of formula (III) acts as a solvent, no
 additional reaction-inert solvent is required. The reaction is optionally carried out in
 the presence of a base such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene,
 sodium bicarbonate, sodiummethanolate and the like. Convenient reaction temperatures
 range between -70°C and reflux temperature.

15

In this and the following preparations, the reaction products may be isolated from the
 reaction medium and, if necessary, further purified according to methodologies
 generally known in the art such as, for example, extraction, crystallization, distillation,
 trituration and chromatography.

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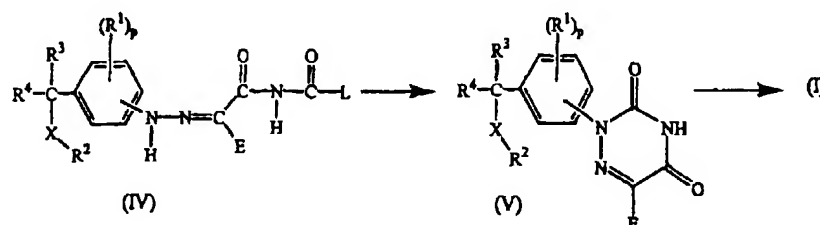
Some of the compounds and intermediates of the present invention can be prepared
 according to or analogous to the procedures described in EP-A-0,170,316,
 EP-A-0,232,932 and WO99/02505.

- 25 Alternatively, for instance, compounds of formula (I) may generally be prepared by
 cyclizing an

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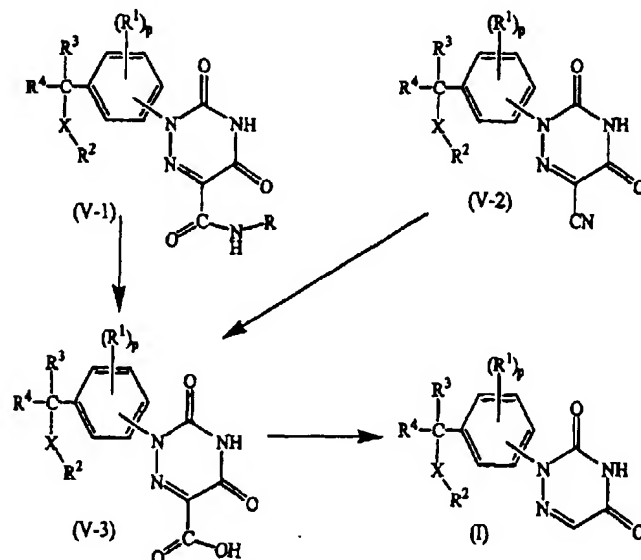
intermediate of formula (IV) wherein L is a suitable leaving group such as, for example, C_{1-6} alkyloxy or halo, and E represents an appropriate electron attracting group such as, for example, an ester, an amide, a cyanide, C_{1-6} alkylsulfonyloxy and the like groups; and eliminating the group E of the thus obtained triazinedione of formula (V).

- 5 The cyclization can suitably be carried out by refluxing the intermediate (IV) in acidic medium such as acetic acid and in the presence of a base such as, for example, potassium acetate.



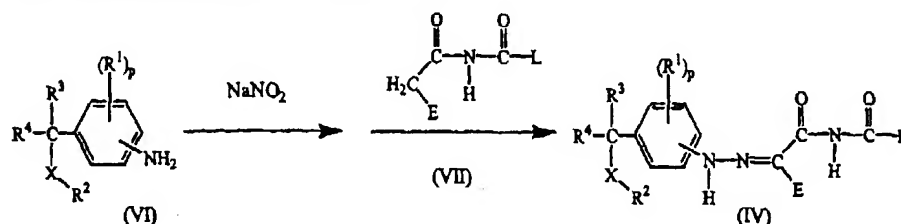
Depending on its nature, E can be eliminated using various art-known elimination

- 10 procedures. For example when E is an amide or a cyano moiety, it can be hydrolyzed to a carboxylic moiety by for instance refluxing the intermediate bearing the E group in hydrochloric acid and acetic acid. The thus obtained intermediate can then be further reacted with mercaptoacetic acid or a functional derivative thereof to obtain a compound of formula (I). Said reaction is conveniently carried out at elevated
- 15 temperatures ranging up to reflux temperature.



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- A suitable way to prepare intermediates of formula (IV) involves the reaction of an intermediate of formula (VI) with sodium nitrate or a functional derivative thereof in an acidic medium such as for example hydrochloric acid in acetic acid, and preferably in the same reaction mixture, further reacting the thus obtained intermediate with a
- 5 reagent of formula (VII) wherein L and E are as defined above, in the presence of a base such as, for example, sodium acetate.

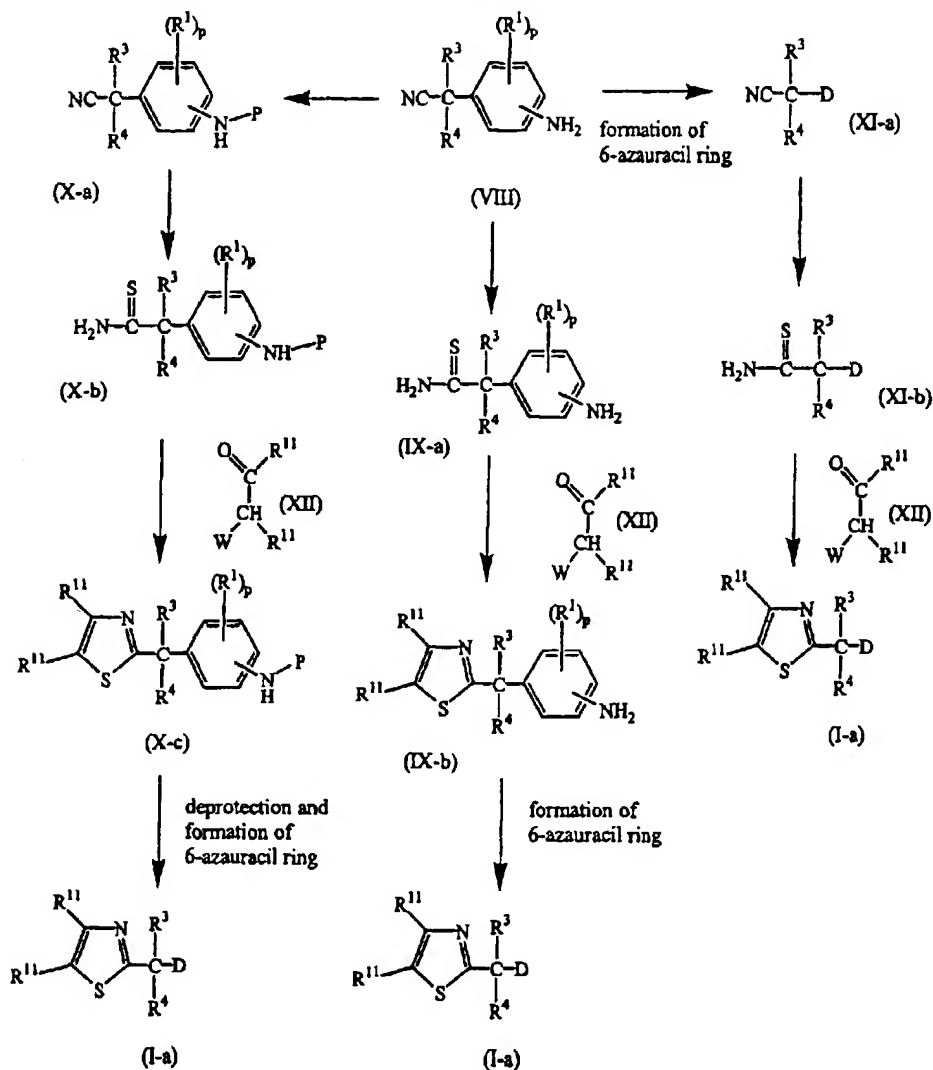


- An interesting subgroup within the present invention are those compounds of formula (I) wherein -X-R² is an optionally substituted 2-thiazolyl moiety, said compounds
- 10 being represented by formula (I-a). The optionally substituted 2-thiazolyl moiety can be incorporated in the compounds of formula (I-a) at different stages of the preparation process.

For instance, scheme 1 depicts three possible ways to prepare compounds of formula (I-a).

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Scheme 1



A first pathway involves the reaction of the cyano moiety in an intermediate of formula (VIII) to the corresponding thioamide using H_2S gas in a suitable solvent such as, for example, pyridine and in the presence of a base such as, for example, triethylamine, thus obtaining an intermediate of formula (IX-a). This thioamide can then be cyclized with an intermediate of formula (XII) wherein W is a suitable leaving group such as, for example, a halogen, e.g. bromo, in a suitable solvent such as, for example, ethanol. The amino moiety in the resulting 2-thiazolyl derivative of formula (IX-b) can then be further reacted as described hereinabove to form a 6-azauracil ring, thus obtaining a compound of formula (I-a).

A second pathway to form compounds of formula (I-a) involves first the protecting of the amino moiety in an intermediate of formula (VIII) by introducing a suitable protective group P such as, for example, an alkylcarbonyl group, using art-known protection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (VII) can be reacted with the corresponding anhydride of formula alkyl-C(=O)-O-C(=O)-alkyl in an appropriate solvent such as, for example, toluene. The thus obtained intermediate of formula (X-a) can then be further reacted according to the first pathway described hereinabove. The final step, before formation of the 6-azauracil ring can be initiated after having deprotected the amino moiety using art-known deprotection techniques. In the example of P being a alkylcarbonyl group, the intermediates of formula (X-c) may be deprotected by reacting them in a suitable solvent such as, for example, ethanol, in the presence of an acid such as, for example, hydrochloric acid.

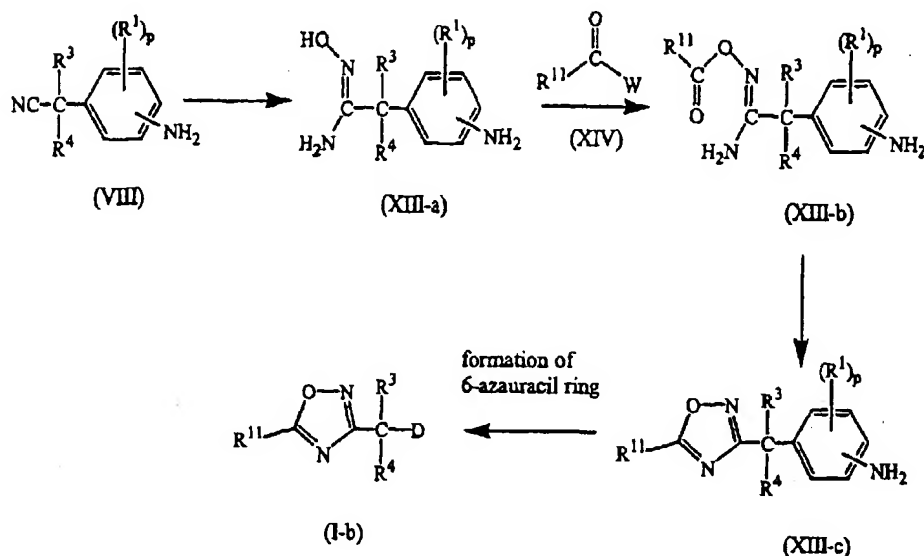
A third pathway involves first the formation of the 6-azauracil ring as described hereinabove but starting from an intermediate of formula (VIII), and subsequently reacting the thus formed intermediate of formula (XI-a) with H_2S and further reacting the thioamide of formula (XI-b) with an intermediate of formula (XII) as described in the first pathway, to finally form a compound of formula (I-a).

Another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X-R^1$ is an optionally substituted 1,2,4-oxadiazol-3-yl moiety, said compounds being represented by formula (I-b-1). The optionally substituted 1,2,4-oxadiazol-3-yl moiety can be incorporated at the same stages of the reaction procedure as depicted for the 2-thiazolyl derivatives in scheme 1.

For instance, analogous to one of the three pathways shown in scheme 1, compounds of formula (I-b) can be performed by reacting an intermediate of formula (VIII) as depicted in scheme 2.

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Scheme 2



In said scheme 2, the cyano group of an intermediate of formula (VIII) is reacted with hydroxylamine or a functional derivative thereof in a suitable solvent such as, for example, methanol, and in the presence of a base such as, for example sodium

5 methanolate. The thus formed intermediate of formula (XIII-a) is then reacted with an intermediate of formula (XIV) wherein W is a suitable leaving group such as, for example, a halogen, e.g. chloro, in an appropriate solvent such as, for example, dichloromethane, and in the presence of a base, such as, for example, *N,N*-(1-methyl-ethyl)ethanamine. The resulting intermediate of formula (XIII-b) is then cyclized to a

10 3-oxadiazolyl derivative of formula (XIII-c). The amino moiety in the intermediates of formula (XIII-c) can then be transformed to the 6-azauracil ring as described above.

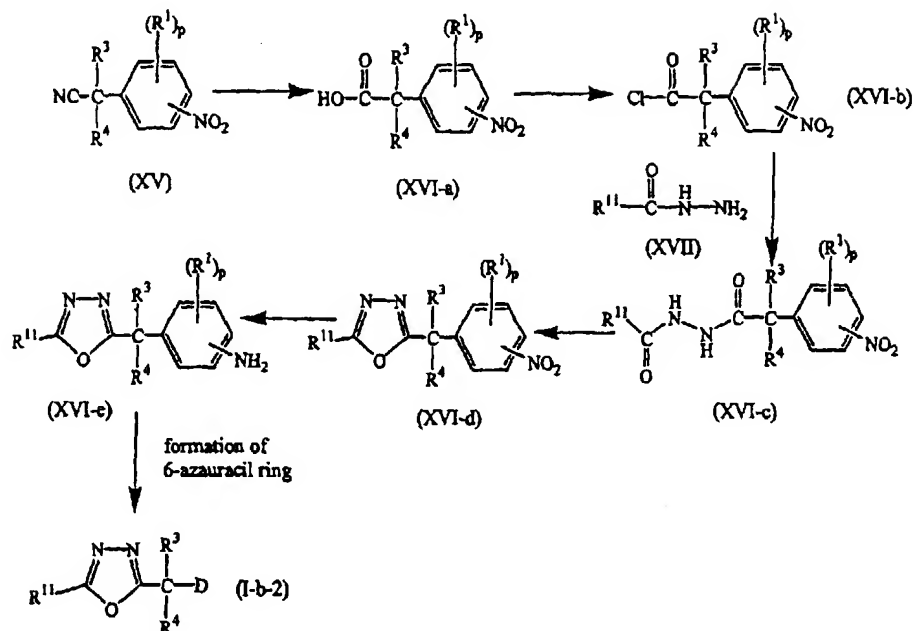
Still another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X-R^2$ is an optionally substituted 1,3,4-oxadiazol-2-yl moiety, said

15 compounds being represented by formula (I-b-2).

For instance, compounds of formula (I-b-2) can be prepared as depicted in scheme 3.

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Scheme 3

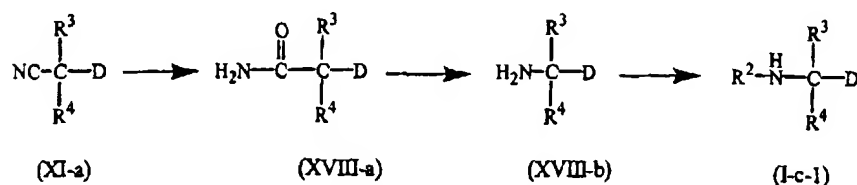


- The nitrile moiety in an intermediate of formula (XV) is transformed into a carboxylic acid moiety using art-known techniques. For instance, the nitrile derivative may be refluxed in a mixture of sulfuric acid and acetic acid in water. The carboxylic acid derivative of formula (XVI-a) may be further reacted with a chlorinating agent such as, for example, thionyl chloride, to form an acylchloride derivative of formula (XVI-b). Subsequently, the acyl chloride may be reacted with a hydrazine derivative of formula (XVII) in a suitable solvent such as, for example, dichloromethane, and in the presence of a base such as, for example, *N,N*-(1-methylethyl)ethanamine. The thus formed intermediate of formula (XVI-c) may be cyclized to a 1,2,4-oxadiazol-2-yl derivative of formula (XVI-d) in the presence of phosphoryl chloride. As a final step before the formation of the 6-azauracil ring as described above, the nitro group in the intermediates of formula (XVI-e) is reduced to an amino group using art-known reduction techniques such as, for instance, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel.

Yet another interesting subgroup within the present invention are those compounds of formula (I) wherein $-X-R^2$ is $-NH-R^2$, said compounds being represented by formula (I-c-1). Scheme 4 depicts a suitable pathway to obtain compounds of formula (I-c-1).

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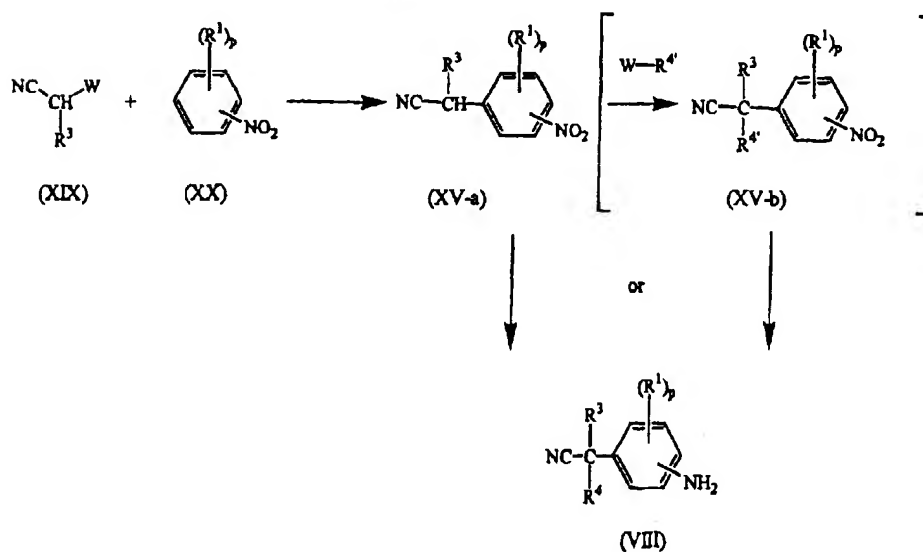
Scheme 4



- In said scheme 4, the cyano moiety of an intermediate of formula (XI-a) is hydrolyzed to the corresponding amide using art-known techniques such as, for instance, hydrolysis in the presence of acetic acid and sulfuric acid. The thus formed amide in the intermediates of formula (XVIII-a) can be transformed in an amine using (diacetoxyiodo)benzene or a functional derivative thereof in a suitable solvent such as, for example a mixture of water and acetonitrile. The amine derivative of formula (XVIII-b) can then be reacted with benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate as described in Tetrahedron Letters No.14 (1975) 1219-1222 to obtain a compound, or with a functional derivative thereof such as, for instance, an isothiocyanate, in an appropriate solvent such as, for example, tetrahydrofuran.

Intermediates of formula (VIII) can be prepared as depicted in scheme 5.

Scheme 5



An intermediate of formula (XIX) and an intermediate of formula (XX) may be reacted in a suitable solvent such as, for example, dimethylsulfoxide, in the presence of a base

such as, for example sodium hydroxide, to form an intermediate of formula (XV-a). The nitro moiety in the intermediates of formula (XV-a) may either be immediately reduced to an amino group using art-known reduction techniques such as, for example, reducing the nitro group with hydrogen in methanol and in the presence of a catalyst such as Raney Nickel, or may first be reacted with an intermediate of formula $R''-W$ wherein R'' is the same as R' but other than hydrogen and W is a suitable leaving group such as, for example, a halogen, e.g. iodo, in a suitable solvent such as, for example, *N,N*-dimethylformamide, and in the presence of a suitable base such as, for example, sodium hydride, before reducing the nitro moiety.

10

The compounds of formula (I) can also be converted into each other following art-known procedures of functional group transformation such as, for example, those mentioned in WO99/02505 and the ones exemplified in the experimental part hereinafter.

15

The compounds of formula (I) may also be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with 3-phenyl-2-(phenylsulfonyl)oxaziridine or with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboxoperoxoic acid or halo substituted benzenecarboxoperoxoic acid, e.g. 3-chlorobenzenecarboxoperoxoic acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *t*-butyl hydroperoxide. Suitable solvents are, for example, water, lower alkanols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

20

25

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g. counter-current distribution, liquid chromatography and the like.

30

Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials as used in the reaction procedures mentioned hereinabove are known compounds and may be commercially available or may be prepared according to art-known procedures.

IL-5, also known as eosinophil differentiating factor (EDF) or eosinophil colony stimulating factor (Eo-CSF), is a major survival and differentiation factor for eosinophils and therefore thought to be a key player in eosinophil infiltration into tissues. There is ample evidence that eosinophil influx is an important pathogenic event in bronchial asthma and allergic diseases such as, cheilitis, irritable bowel disease, eczema, urticaria, vasculitis, vulvitis, winterfeet, atopic dermatitis, pollinosis, allergic rhinitis and allergic conjunctivitis; and other inflammatory diseases, such as eosinophilic syndrome, allergic angitis, eosinophilic fasciitis, eosinophilic pneumonia,

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PIE syndrome, idiopathic eosinophilia, eosinophilic myalgia, Crohn's disease, ulcerative colitis and the like diseases.

The present compounds also inhibit the production of other chemokines such as monocyte chemotactic protein-1 and -3 (MCP-1 and MCP-3). MCP-1 is known to attract both T-cells, in which IL-5 production mainly occurs, and monocytes, which are known to act synergetically with eosinophils (Carr et al., 1994, Immunology, 91, 3652-3656). MCP-3 also plays a primary role in allergic inflammation as it is known to mobilize and activate basophil and eosinophil leukocytes (Baggiolini et al., 1994, Immunology Today, 15(3), 127-133).

The present compounds have no or little effect on the production of other chemokines such as IL-1, IL-2, IL-3, IL-4, IL-6, IL-10, γ -interferon (IFN- γ) and granulocyte-macrophage colony stimulating factor (GM-CSF) indicating that the present IL-5 inhibitors do not act as broad-spectrum immunosuppressives.

The selective chemokine inhibitory effect of the present compounds can be demonstrated by *in vitro* chemokine measurements in human blood. *In vivo* observations such as the inhibition of eosinophilia in mouse ear, the inhibition of blood eosinophilia in the *Ascaris* mouse model; the reduction of serum IL-5 protein production and splenic IL-5 mRNA expression induced by anti-CD3 antibody in mice and the inhibition of allergen- or Sephadex-induced pulmonary influx of eosinophils in guinea-pig are indicative for the usefulness of the present compounds in the treatment of eosinophil-dependent inflammatory diseases.

The present inhibitors of IL-5 production are particularly useful for administration via inhalation.

The intermediates of formula (XI-a) are interesting intermediates. Not only have they a particular usefulness as intermediates in the preparation of the compounds of formula (I), they also have valuable pharmacological activity.

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In view of the above pharmacological properties, the compounds of formula (I) can be used as a medicine. In particular, the present compounds can be used in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases as mentioned hereinabove, more in particular bronchial asthma, atopic dermatitis, 5 allergic rhinitis and allergic conjunctivitis.

In view of the utility of the compounds of formula (I), there is provided a method of treating warm-blooded animals, including humans, suffering from eosinophil-dependent inflammatory diseases, in particular bronchial asthma, atopic dermatitis, 10 allergic rhinitis and allergic conjunctivitis. Said method comprises the systemic or topical administration of an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

15 The present invention also provides compositions for treating eosinophil-dependent inflammatory diseases comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

To prepare the pharmaceutical compositions of this invention, a therapeutically 20 effective amount of the particular compound, in base form or addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for systemic administration such as parenteral 25 administration; or topical administration such as via inhalation, a nose spray or the like. Application of said compositions may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular, semisolid compositions such as salves, creams, gellies, ointments and the 30 like will conveniently be used.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

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Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are

5 tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In order to enhance the solubility and/or the stability of the compounds of formula (I) in

10 pharmaceutical compositions, it can be advantageous to employ α -, β - or γ -cyclodextrins or their derivatives. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds of formula (I) in pharmaceutical compositions. In the preparation of aqueous compositions, addition salts of the subject compounds are obviously more suitable due to their increased water solubility.

15 Appropriate cyclodextrins are α -, β -, γ -cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β -CD; hydroxy C_{1-6} alkyl, particularly hydroxyethyl, hydroxy-

20 propyl or hydroxybutyl; carboxy C_{1-6} alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6} alkylcarbonyl, particularly acetyl; C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy- C_{1-6} alkyloxy C_{1-6} alkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; C_{1-6} alkylcarbonyloxy C_{1-6} alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β -CD, randomly methylated β -CD,

25 2,6-dimethyl- β -CD, 2-hydroxyethyl- β -CD, 2-hydroxyethyl- γ -CD, 2-hydroxypropyl- γ -CD and (2-carboxymethoxy)propyl- β -CD, and in particular 2-hydroxypropyl- β -CD (2-HP- β -CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two

30 cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

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The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the M.S. ranges from 0.125 to 10.

5

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques, preferably, as measured by mass spectrometry, the D.S. ranges from 0.125 to 3.

10

Due to their high degree of selectivity as IL-5 inhibitors, the compounds of formula (I) as defined above, are also useful to mark or identify receptors. To this purpose, the compounds of the present invention need to be labelled, in particular by replacing, partially or completely, one or more atoms in the molecule by their radioactive isotopes. Examples of interesting labelled compounds are those compounds having at least one halo which is a radioactive isotope of iodine, bromine or fluorine; or those compounds having at least one ^{11}C -atom or tritium atom.

15

One particular group consists of those compounds of formula (I) wherein R^3 and/or R^4 are a radioactive halogen atom. In principle, any compound of formula (I) containing a halogen atom is prone for radiolabelling by replacing the halogen atom by a suitable isotope. Suitable halogen radioisotopes to this purpose are radioactive iodides, e.g. ^{122}I , ^{123}I , ^{125}I , ^{131}I ; radioactive bromides, e.g. ^{75}Br , ^{76}Br , ^{77}Br and ^{82}Br , and radioactive fluorides, e.g. ^{18}F . The introduction of a radioactive halogen atom can be performed by a suitable exchange reaction or by using any one of the procedures as described hereinabove to prepare halogen derivatives of formula (I).

25

Another interesting form of radiolabelling is by substituting a carbon atom by a ^{11}C -atom or the substitution of a hydrogen atom by a tritium atom.

30

Hence, said radiolabelled compounds of formula (I) can be used in a process of specifically marking receptor sites in biological material. Said process comprises the

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steps of (a) radiolabelling a compound of formula (I), (b) administering this radio-labelled compound to biological material and subsequently (c) detecting the emissions from the radiolabelled compound. The term biological material is meant to comprise every kind of material which has a biological origin. More in particular this term refers to tissue samples, plasma or body fluids but also to animals, specially warm-blooded animals, or parts of animals such as organs.

The radiolabelled compounds of formula (I) are also useful as agents for screening whether a test compound has the ability to occupy or bind to a particular receptor site. The degree to which a test compound will displace a compound of formula (I) from such a particular receptor site will show the test compound ability as either an agonist, an antagonist or a mixed agonist/antagonist of said receptor.

When used in *in vivo* assays, the radiolabelled compounds are administered in an appropriate composition to an animal and the location of said radiolabelled compounds is detected using imaging techniques, such as, for instance, Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) and the like. In this manner the distribution of the particular receptor sites throughout the body can be detected and organs containing said receptor sites can be visualized by the imaging techniques mentioned hereinabove. This process of imaging an organ by administering a radiolabelled compound of formula (I) and detecting the emissions from the radioactive compound also constitutes a part of the present invention.

In general, it is contemplated that a therapeutically effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, in particular from 0.05 mg/kg to 10 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

Experimental part

In the examples hereinafter, "DMSO" stands for dimethylsulfoxide, "RT" stands for room temperature, "DMF" stand for *N,N*-dimethylformamide, "EtOAc" stands for ethylacetate, "DIPE" stands for diisopropylether and "THF" stands for tetrahydrofuran.

A. Preparation of the intermediate compounds

Example A1

- a) A mixture of 2-chloropropionitrile (0.2 mol) and 1,3-dichloro-5-nitrobenzene (0.2 mol) in DMSO (50ml) was added dropwise at RT to a solution of NaOH (1 mol) in DMSO (150ml) while the temperature was kept below 30°C. The mixture was stirred at RT for 1 hour, then poured out on ice and acidified with HCl. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂. The organic solution was washed with H₂O, dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/cyclohexane 70/30). The pure fractions were collected and the solvent was evaporated, yielding 19.5 g (40%) of (±)-2,6-dichloro-α-methyl-4-nitrobenzeneacetonitrile (interm. 1).
- b) NaH 80% (0.0918 mol) was added portionwise at 0°C under N₂ flow to a solution of intermediate (1) (0.0612 mol) in DMF (100ml). The mixture was stirred at 0°C under N₂ flow for 1 hour. CH₃I (0.0918 mol) was added dropwise at 0°C. The mixture was stirred at 50°C for 12 hours, then poured out on ice and extracted with EtOAc. The organic layer was separated, washed with H₂O, dried, filtered and the solvent was evaporated, yielding 17.1g of 2,6-dichloro-α,α-dimethyl-4-nitrobenzeneacetonitrile (interm. 2).
- c) A mixture of intermediate (2) (0.066 mol) in CH₃OH (200ml) was hydrogenated at RT under a 3 bar pressure for 1 hour with Raney Nickel (15g) as a catalyst. After uptake of H₂, the catalyst was filtered through celite, washed with CH₃OH and the filtrate was evaporated, yielding 17.1 g of 4-amino-2,6-dichloro-α,α-dimethylbenzeneacetonitrile (interm. 3).

Example A2

- a) A solution of NaNO₂ (0.36 mol) in H₂O (50 ml) was added to a solution of intermediate (3) (0.34 mol) in acetic acid (700 ml) and HCl (102 ml), stirred at 10°C. The reaction mixture was stirred for 80 minutes at 10°C. A powdered mixture of sodium acetate (1.02 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.374 mol) was added and the reaction mixture was stirred for 40 minutes. The reaction mixture was poured out onto crushed ice. The precipitate was filtered off, washed with water, taken up into CH₂Cl₂, and the layers were separated. The organic layer was dried, filtered and the solvent evaporated, yielding 138.5 g (84%) of diethyl N,N'-

-29-

[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]dicarbamate (interm. 4).

b) A solution of intermediate (4) (0.28 mol) and potassium acetate (0.28 mol) in acetic acid (1000 ml) was stirred and refluxed for 3 hours. The reaction mixture containing
5 ethyl [[2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 5) was used as such in the next step.

c) Intermediate (5) (crude reaction mixture) was treated with HCl 36% (0.84 mol). The reaction mixture was stirred and refluxed for 4 hours, then stirred at RT over the
10 weekend. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated, yielding 111.6 g of 2-[[3,5-dichloro-4-(1-cyano-1-methylethyl)phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 6).

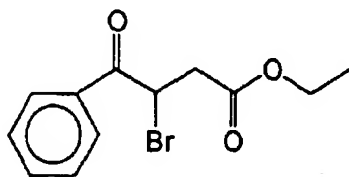
d) A suspension of intermediate (6) (0.28 mol) in mercaptoacetic acid (250.0 ml) was
15 stirred for 4 hours at 100 °C, then allowed to cool to RT and stirred overnight. The reaction mixture was poured out onto crushed ice and this mixture was extracted with CH₂Cl₂. The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue was purified by short column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The
20 pure fractions were collected and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, then dried, yielding 36.8 g (41%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)- α,α -dimethylbenzene-acetonitrile. The filtrate was stirred in DIPE and the resulting precipitate was filtered off, washed with DIPE, and dried, yielding 2.5 g (3%) of 2,6-dichloro-4-(4,5-dihydro-
25 3,5-dioxo-1,2,4-triazin-2(3*H*)-yl)- α,α -dimethylbenzeneacetonitrile (interm. 7).

e) A solution of intermediate (7) (0.107 mol) and *N,N*-bis(1-methylethyl)ethanamine (0.315 mol) in pyridine (500 ml) was stirred and heated to 80°C. H₂S was allowed to bubble through this solution for 24 hours at 80°C. H₂S gas inlet was stopped and the reaction mixture was stirred over the weekend at RT. The solvent was evaporated.
30 CH₂Cl₂/CH₃OH (500 ml; 9:1) was added, and this mixture was poured out into 2 N HCl (1000 ml) at 0°C. The mixture was stirred for 10 minutes. The precipitate was filtered off and dried, yielding 23.2 g (64%) of 2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4)- α,α -dimethylbenzeneethanethioamide (interm. 8).

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Example A3

Reaction under N₂ atmosphere. A solution of intermediate (8) (0.0125 mol) and



(0.0157 mol) in ethanol (60 ml) and DMF (30 ml;

dried over molecular sieves) was stirred for 6.5 hours at 60 °C, then overnight at RT.

- 5 The solvent was evaporated. The residue was taken up into water (100 ml) and this mixture was extracted with CH₂Cl₂ (100 ml). The separated organic layer was dried (MgSO₄), filtered and the solvent evaporated, then co-evaporated with toluene. The residue (13 g) was purified by flash column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 100/0, then 99/1, ending with 98/2). The desired fractions were
- 10 collected and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator. The residue (6.5 g) was crystallized from CH₃CN. The precipitate was filtered off, washed with CH₃CN and DIPE, then dried (vacuum, 50 °C), yielding 3.17 g (46.5 %) of ethyl-2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)]phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetate (intermediate 9) having a
- 15 melting point of 148°C.

Example A4

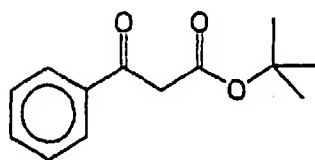
A mixture of intermediate (9) (0.00183 mol) and NaOH 1N (0.0055 mol) in CH₃OH (25 ml) and THF (25 ml) was stirred overnight at RT. The reaction mixture was

- 20 acidified with 1N HCl (8 ml), and the product was taken up into EtOAc. The organic layer was washed with brine, dried, filtered and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off, washed with DIPE, and dried, yielding 0.8 g (79%) of 2-[1-[2,6-dichloro-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl)]phenyl]-1-methylethyl]-4-phenyl-5-thiazoleacetic acid
- 25 (intermediate (10)).

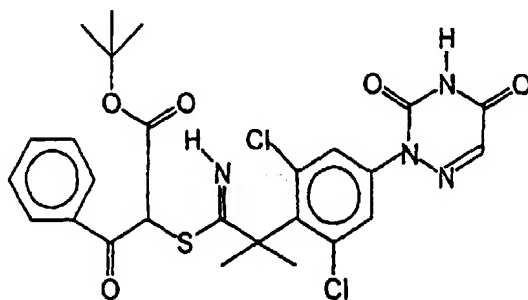
Example A5

First a solution of bromine (0.02 mol) in CH₂Cl₂ (20 ml) was added dropwise at 10°C under N₂ flow to a mixture of a compound of formula

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(0.0227 mol) in CH_2Cl_2 (50ml). The mixture was stirred at 10°C for 1 hour. H_2O and solid K_2CO_3 were added. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The reaction was carried out 4 times, using the same quantities and combining the residues yielding 14 g (51%) of 1,1-dimethylethyl α -bromo- β -oxo-benzenepropanoate. A mixture of intermediate (8) (0.0119 mol), 1,1-dimethylethyl α -bromo- β -oxo-benzenepropanoate (0.0137 mol) and K_2CO_3 (0.0357 mol) in CH_3CN (55ml) was stirred at room temperature for 3.5 hours. Ice and EtOAc were added. The mixture was acidified with HCl 3N. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The product was used without further purification. Yielding: 8g of intermediate 11 having the formula

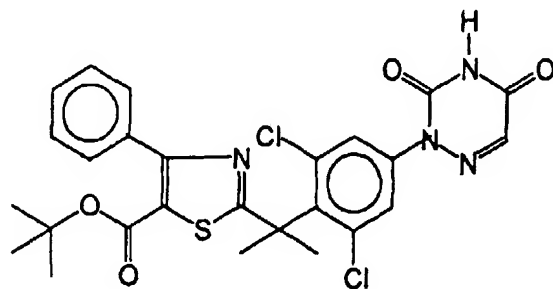


20 Example A6

Intermediate (11) (0.0119 mol) and tert.-butanol (24g) were stirred and refluxed for 2 hours. The mixture was brought to room temperature. The solvent was evaporated. The residue was taken up in CH_2Cl_2 . The organic solution was washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (7.8g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1; 15-40 μm). Two fractions were collected and their solvents were evaporated. Yielding: 2.66g (fraction 1) and 0.7g fraction 2 (50%). Fraction 2 was purified by column chromatography over C 18 (eluent: $\text{CH}_3\text{OH}/\text{NH}_4\text{OAc}$ 0.5% 80/20; column: HYPERSIL C 18 3 μm). The pure fractions were collected and the solvent was

-32-

evaporated. Yielding: 0.45g of intermediate 12 having a melting point of 130°C and represented by the formula

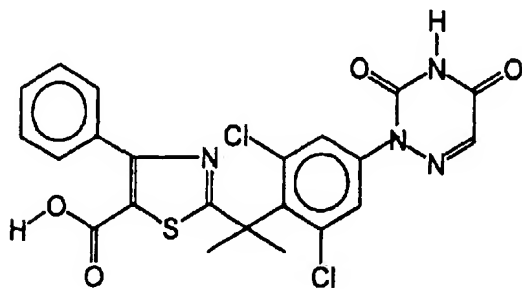


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Example A7

Intermediate 12 (0.00465 mol) was added portionwise at 0°C-10°C to trifluoroacetic acid (35ml). The mixture was stirred at room temperature for 3 hours and poured out into H₂O. The precipitate was filtered off, washed with H₂O and taken up in CH₂Cl₂.

- 10 The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.4g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 97/3/0.2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN. The precipitate was filtered off and dried. Yielding: 1.16g of intermediate 13 having a
- 15 melting point of 232°C and represented by the formula

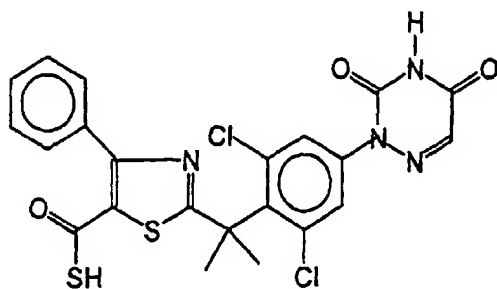


Example A8

- 1,1'-carbonylbis-1H-imidazole (0.0159 mol) was added portionwise at RT under N₂ flow to a solution of intermediate (13) (0.00795 mol) in DMF (60 ml). The mixture
- 20 was stirred at RT overnight. H₂S was bubbled through the mixture for 1 hour. The mixture was stirred at RT for 1 hour, poured out into a saturated NaCl solution and

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extracted twice with CH_2Cl_2 . The combined organic layer was dried (MgSO_4), filtered and the solvent was evaporated. The product, interm. 14 represented by the formula

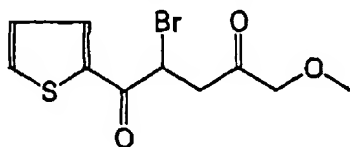


5

was used without further purification.

Example A9

A mixture of intermediate (8) (0.0158 mol) and



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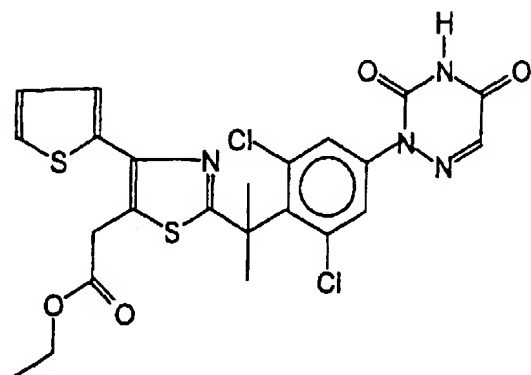
(0.0237 mol) in ethanol (60ml) and DMF (40ml)

was stirred at 60°C for 4 hours. The solvent was evaporated. EtOAc was added. The organic solution was washed 3 times with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (11.2g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm). The desired fractions were

15

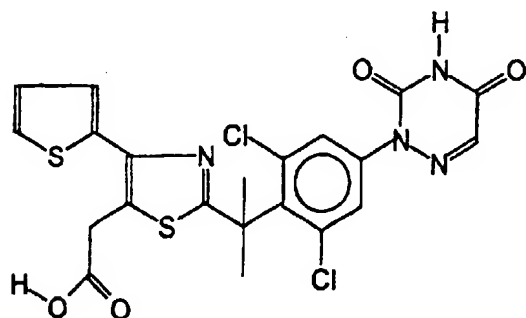
collected and the solvent was evaporated. Yielding: 4.2g (47%). Part of this fraction (1.5g) was crystallized from petroleum ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.15g of intermediate 15 having a melting point of 126°C and represented by the formula

-34-



10 Example A10

A mixture of intermediate (15) (0.0045 mol) and NaOH (0.0135 mol) in methanol (30ml) and THF (30ml) was stirred at room temperature for 12 hours, poured out on ice, acidified with HCl and extracted with EtOAc. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue (2.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH/NH₄OH 95/5/0.1; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 1.5g (64%). Part of this fraction (1g) was crystallized from diethyl ether. The precipitate was filtered off and dried. Yielding: 0.5g of intermediate 16 having a melting point of 192°C and represented by the formula



20

Example A11

a) NaOCH₃, 30% (0.592 mol) was added to a solution of hydroxylamine hydrochloride (0.1085 mol) in CH₃OH (200 ml), stirred at RT. The mixture was stirred for 10 minutes. Intermediate (3) (0.0542 mol) was added portionwise and the resulting reaction mixture was stirred and refluxed overnight. The solvent was evaporated. The residue was partitioned between CH₂Cl₂ and water. The organic layer was separated,

dried, filtered and the solvent was evaporated. The residue was stirred in DIPE, filtered off, washed with DIPE, and dried, yielding 3.7 g of (26%) 4-amino-2,6-dichloro-*N*-hydroxy- α,α -dimethylbenzeneethanimidamide (intern. 17).

b) A solution of intermediate (17) (0.0323 mol) and *N,N*-bis(methylethyl)ethanamine (0.0339 mol) in CH_2Cl_2 (190 ml) was stirred at 15°C. A solution of 2-methylbenzoyl chloride (0.0323 mol) in CH_2Cl_2 (10 ml) was added dropwise and the resulting reaction mixture was stirred for one hour. Water was added. The organic layer was separated, dried, filtered and the solvent was evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding 13.0 g of [1-amino-2-(4-amino-2,6-dichlorophenyl)-2-methylpropylidene]amino 2-methylbenzoate (intern. 18).

c) A solution of intermediate (18) (0.0323 mol) and *p*-toluenesulfonic acid (0.0323 mol) in DMSO (100 ml) was stirred for 30 minutes at 150°C. The reaction mixture was cooled. Water was added and this mixture was extracted with toluene. The separated organic layer was dried, filtered and the solvent evaporated. The residue was purified by short column chromatography over silica gel (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The concentrate was co-evaporated with EtOAc, yielding 11.7 g of 3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]benzenamine (intern. 19).

d) A solution of intermediate (19) (0.0302 mol) and HCl conc. (0.0906 mol) in acetic acid (100 ml) was stirred at 0°C. A solution of NaNO_2 (0.032 mol) in water (10 ml) was added dropwise at 0°C. The reaction mixture was stirred for 1 hour at 0°C. A powdered mixture of sodium acetate (0.0906 mol) and diethyl(1,3-dioxo-1,3-propanediyl)biscarbamate (0.0332 mol) was added portionwise. The mixture was allowed to warm to RT and stirred for 1 hour. Water was added and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding diethyl *N,N*-[2-[[3,5-dichloro-4-[1-[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]hydrazono]-1,3-dioxo-1,3-propanediyl]-dicarbamate (intern. 20).

e) A solution of intermediate (20) (0.0302 mol) and sodium acetate (0.0302 mol) in acetic acid (200 ml) was stirred and refluxed for 3 hours. The reaction mixture was poured out into water and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated. Toluene was added and azeotroped on the rotary evaporator, yielding ethyl [[2-[3,5-dichloro-4-[1-[5-(2-methyl-

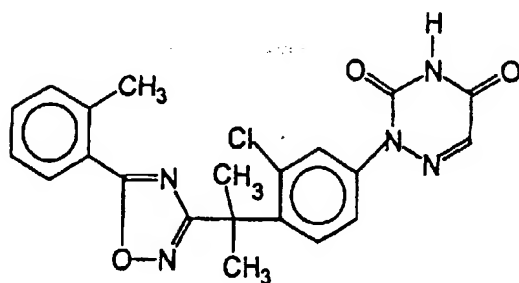
-36-

phenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazin-6-yl]carbonyl]carbamate (interm. 21).

- f) A mixture of intermediate (21) (0.0302 mol) in HCl 36% (10 ml) and acetic acid (200 ml) was stirred and refluxed overnight. The reaction mixture was poured out onto
5 crushed ice and this mixture was extracted with CH_2Cl_2 . The separated organic layer was dried, filtered and the solvent evaporated, yielding 16.3 g of 2-[3,5-dichloro-4-[1-[5-[2-methylphenyl)-1,2,4-oxadiazol-3-yl]-1-methylethyl]phenyl]-2,3,4,5-tetrahydro-3,5-dioxo-1,2,4-triazine-6-carboxylic acid (interm. 22).

Example A12

- 10 A mixture of intermediate (22) (0.0133 mol) in mercaptoacetic acid (7ml) was stirred at 175°C for 2 hours. The mixture was cooled, poured out into ice water, basified with K_2CO_3 and extracted with EtOAc. The organic layer was separated, washed with H_2O , dried, filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 99/1). The pure fractions were
15 collected and the solvent was evaporated, yielding 2.2g (36%) of intermediate 23 represented by the formula

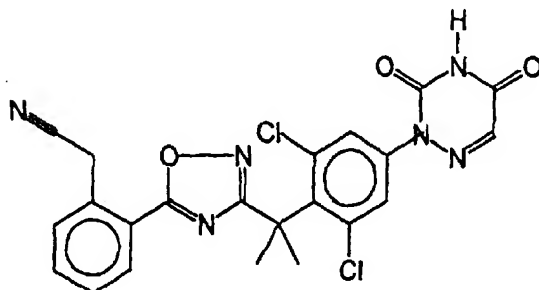


20 Example A13

- A mixture of intermediate (23) (0.0011 mol), 1-bromo-2,5-pyrrolinedione (0.0011 mol) and dibenzoyl peroxide (catalytic quantity) in CCl_4 (30 ml) was stirred and refluxed for 3 hours. The mixture was allowed to cool to RT. The mixture was filtered over
dicalite and the filtrate contained 2-[4-[1-[5-[2-(bromomethyl)phenyl]-1,2,4-oxadiazol-
25 3-yl]-1-methylethyl]-3,5-dichlorophenyl]-1,2,4-triazine-3,5(2*H*,4*H*)-dione
(intermediate 24).

Example A14

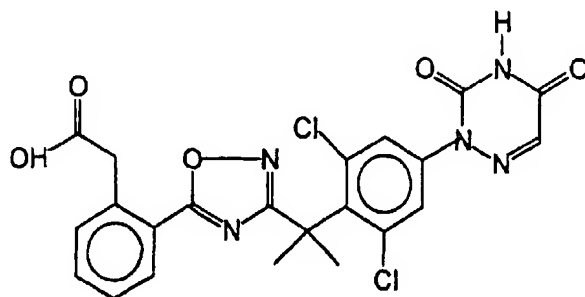
A solution of intermediate (24) (0.017 mol) and KCN (0.034 mol) in ethanol (100 ml) and H₂O (30 ml) was stirred for 8 hours at 60°C. The solvent was evaporated under reduced pressure. The residue was taken up into CH₂Cl₂, then washed with water, dried (MgSO₄), filtered and the solvent was evaporated. Yield: 8.2 g of interm.25 represented by the formula



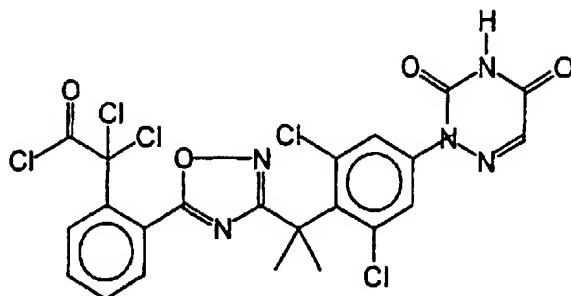
10 Example A15

A solution of intermediate (25) (0.017 mol) in HOAc (50 ml), H₂SO₄ (50 ml) and H₂O (50 ml) was stirred and refluxed for 2 hours. The reaction mixture was poured out into ice-water and the resulting precipitate was filtered off, washed, then dissolved in CH₂Cl₂. The organic solution was dried, filtered and the solvent was evaporated. The residue was purified over silica gel on a glass filter (eluent: CH₂Cl₂/CH₃OH 95/5). The desired fractions were collected and the solvent was evaporated. The residue was purified by HPLC over RP BDS Hyperprep C18 (100 Å =, 8 µm; gradient elution with (0.5% NH₄OAc in water/CH₃CN 90/10)/CH₃OH/CH₃CN). The pure fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off and dried (vacuum, 60 °C). Yield: 0.084 g of intermediate 26 represented by the formula

-38-

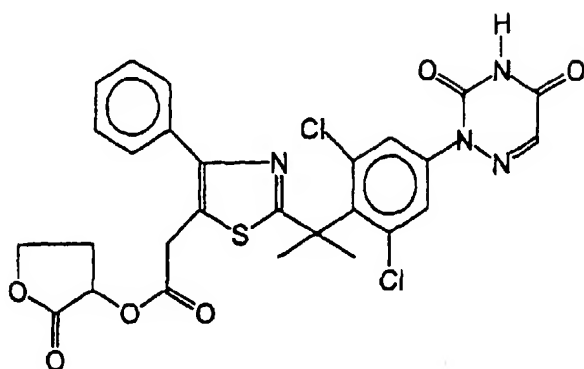
**Example A16**

- A solution of intermediate (26) (0.0014 mol) in SOCl_2 (15 ml) was stirred and refluxed for 1 hour. SOCl_2 was evaporated under reduced pressure. Toluene was added and azeotroped on the rotary evaporator, yielding 100% of intermediate 27 represented by the formula

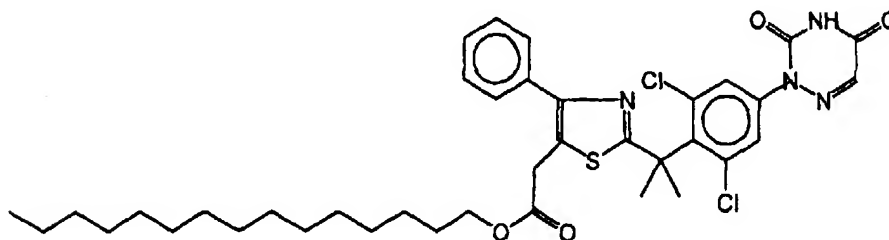
**B. Preparation of the final compounds****Example B1**

- A mixture of 3-bromodihydro-2(3H)-furanone (0.0081 mol) in DMF (16ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00773 mol) and NaHCO_3 (0.0081 mol) in DMF (30ml). The mixture was stirred at 70°C for 5 hours and brought to room temperature. H_2O and a saturated NaCl solution were added. The mixture was extracted with EtOAc. The organic layer was separated, dried (MgSO_4), filtered and the solvent was evaporated. The residue (5g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. The residue was taken up in DIPE. The precipitate was filtered off and dried. Yielding: 1.24g compound 1 having a melting point of 72°C and represented by the formula

-39-

**Example B2**

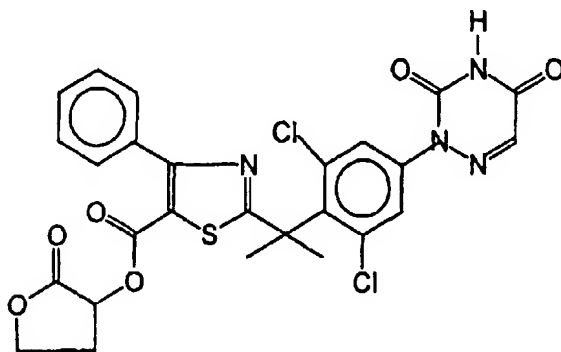
- A solution of 1-bromopentadecane (0.0051 mol) in DMF (18ml) was added dropwise at room temperature to a mixture of intermediate (10) (0.00483 mol) and NaHCO_3 (0.0051 mol) in DMF (10ml). The mixture was stirred at 70°C for 5 hours and at 45°C overnight, then brought to room temperature. H_2O and NaCl was added. The mixture was extracted with EtOAc. The organic layer was separated, washed with a saturated NaCl solution, dried (MgSO_4), filtered and the solvent was evaporated. The residue (3.8g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 98/2; 15-40 μm). The pure fractions were collected and the solvent was evaporated. Yielding: 0.49g compound 2 having a melting point of 80°C and represented by the formula

**Example B3**

- A solution of 3-bromodihydro-2(3H)-furanone (0.0073 mol) in DMF (12ml) was added dropwise at RT to a mixture of intermediate (13) (0.00695 mol) and NaHCO_3 (0.0073 mol) in DMF (22ml). The mixture was stirred at 70°C for 2.5 hours, brought to RT and poured out into H_2O . The precipitate was filtered off and taken up in CH_2Cl_2 . The organic layer was separated, washed with H_2O , dried (MgSO_4), filtered and the solvent was evaporated. The residue (5.4g) was purified by column chromatography over silica

-40-

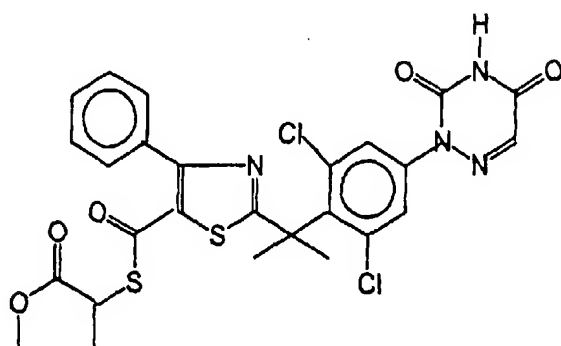
gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μ m). The desired fractions were collected and the solvent was evaporated. The residue was crystallized from CH₃CN, diethyl ether and DIPE. The precipitate was filtered off and dried. Yielding: 1.3g. This fraction was recrystallized from CH₃CN, 2-propanone and diethyl ether. The precipitate was
5 filtered off and dried. Yielding: 0.89g compound 3 having a melting point of 208°C and represented by the formula



Example B4

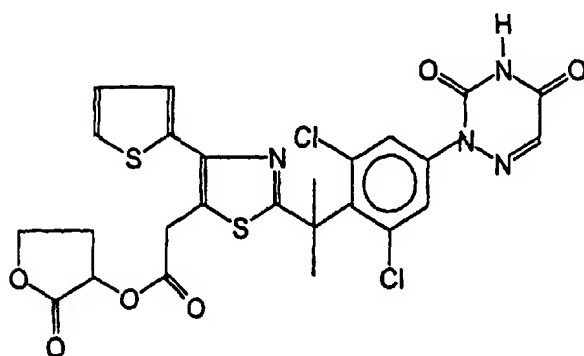
NaHCO₃ (0.00835 mol) was added dropwise at 5°C under N₂ flow to a mixture of
10 intermediate (14) (0.00795 mol) in DMF (22ml). Then a solution of 3-bromodihydro-
2(3H)-furanone (0.00835 mol) in DMF (12ml) was added dropwise. The mixture was
brought to RT and stirred at RT for 30 min and then poured out into H₂O and a
saturated NaCl solution. A small amount of HCl 3N was added. The precipitate was
filtered off and taken up in CH₂Cl₂. The organic layer was separated, dried (MgSO₄),
15 filtered and the solvent was evaporated. The residue (5.1g) was purified by column
chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98.5/1.5; 15-40 μ m). The
pure fractions were collected and the solvent was evaporated. The residue was
crystallized from CH₃CN, diethyl ether and DIPE. The precipitate was filtered off and
dried. The residue was recrystallized from CH₃CN, diethyl ether and DIPE. The
20 precipitate was filtered off and dried. Yielding: 0.85g compound 4 having a melting
point of 212°C and represented by the formula

-41-



Example B5

A mixture of 3-bromodihydro-2(3H)-furanone (0.00172 mol) in DMF (5ml) was added dropwise at RT to a mixture of intermediate (16) (0.00172 mol) and NaHCO₃ (0.00172 mol) in DMF (5ml). The mixture was stirred at 70°C for 5 hours, poured out into H₂O and a saturated NaCl solution and extracted with EtOAc. The organic layer was separated, washed several times with H₂O, dried (MgSO₄), filtered and the solvent was evaporated. The residue (1.2g) was purified by column chromatography over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2; 15-40 μm). The desired fractions were collected and the solvent was evaporated. The residue was purified again by column chromatography over silica gel (eluent: CH₂Cl₂/2-propanol 97/3; 15-40 μm). The desired fractions were collected and the solvent was evaporated. Yielding: 0.13g compound 5 having a melting point of 110°C and represented by the formula

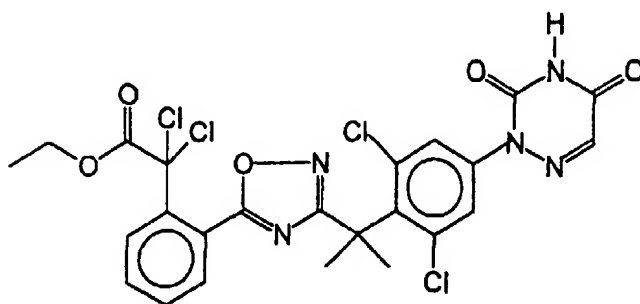


15 Example B6

A solution of intermediate (27) (0.001 mol) in ethanol (15 ml) and dichloromethane (15 ml) was stirred and refluxed for one hour. The solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed with water, dried (MgSO₄),

-42-

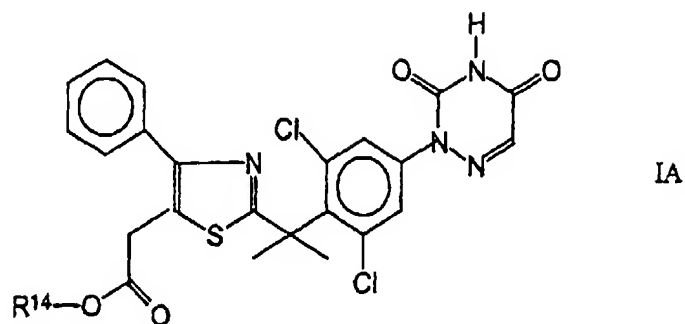
filtered and the solvent was evaporated. The residue was purified by HPLC over Hyperprep C18 (eluent: ((0.5% NH₄OAc in H₂O)/CH₃CN 90/10)/CH₃CN (0 min) 80/20, (44 min) 20/80, (57-61 min) 0/100). The desired fractions were collected and the solvent was evaporated. The residue was stirred in hexane, filtered off, washed and
5 dried (vacuum, 60 °C). Yield: 0.059 g compound 6 having a melting point of 157°C and represented by the formula



Example B7

A mixture of intermediate (10) (0.00387 mol) and 1,1'-carbonylbis-1H-imidazole
10 (0.0058 mol) in dichloromethane (40ml) was stirred at RT for 90 minutes, then cyclohexylmethanol (0.0058 mol) was added. The mixture was stirred at RT overnight, diluted with CH₂Cl₂ and washed twice with an aqueous solution of NaCl. The organic layer was separated, dried (MgSO₄), filtered and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent:
15 CH₂Cl₂/EtOAc 50/50). The pure fractions were collected and the solvent was evaporated. The residue was crystallized from EtOAc. The precipitate was filtered off, washed with DIPE and dried at 50°C overnight. Yielding: 1.43g compound 7 with a melting point of 180°C and represented by the formula

-43-

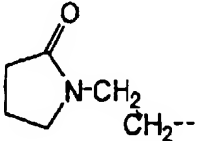
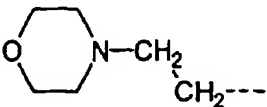


wherein R¹⁴ is cyclohexylmethyl.

The following table 1 lists compounds of formula (1A) which were prepared according to the same procedure.

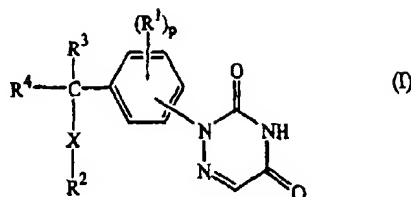
COMPOUND NO.	R ¹⁴	MELTING POINT (°C)
8		
9	Isopentyl	148
10	2-phenyl-ethyl	130
11	3-phenyl-n-propyl	114
12	2-(N,N'-diisopropylamino)-ethyl	136
13	2-cyano-ethyl	179
14		
15	3-cyclohexyl-n-propyl	130

-44-

16	4-phenyl-n-butyl	128
17	Cyclopropylmethyl	
18	3-cyclopropyl-n-propyl	
19		
20		

Claims

1. A compound having the formula



a *N*-oxide, a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein :

p represents an integer being 0, 1, 2, 3 or 4;

X represents O, S, NR⁵ or a direct bond or *X*-R² taken together may represent cyano;

Y represents O, S, NR⁵, or S(O)₂;

each R¹ independently represents C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl,

hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, R⁶, NR⁷R⁸ or C₁₋₄alkyl substituted with C(=O)-Z-R¹⁴, Het³, R⁶ or NR⁷R⁸;

R² represents Het¹, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkyl or C₁₋₆alkyl substituted with one or two substituents selected from C(=O)-Z-R¹⁴, hydroxy, cyano, amino, mono- or di(C₁₋₄alkyl)amino, C₁₋₆alkyloxy optionally substituted with C(=O)-Z-R¹⁴, C₁₋₆alkylsulfonyloxy, C₃₋₇cycloalkyl optionally substituted with C(=O)-Z-R¹⁴, aryl, aryloxy, arylthio, Het¹, Het¹oxy and Het¹thio; and if *X* is O, S or NR⁵, then R² may also represent aminothiocarbonyl, C₁₋₄alkylcarbonyl optionally substituted with C(=O)-Z-R¹⁴, C₁₋₄alkylthiocarbonyl optionally substituted with C(=O)-Z-R¹⁴, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl;

R³ represents hydrogen, C₁₋₄alkyl or C₃₋₇cycloalkyl;

R⁴ represents hydrogen, C₁₋₄alkyl or C₃₋₇cycloalkyl; or

R³ and R⁴ taken together form a C₂₋₆alkanediyl;

R⁵ represents hydrogen or C₁₋₄alkyl;

each R⁶ independently represents C₁₋₆alkylsulfonyl, aminosulfonyl, mono- or di(C₁₋₄alkyl)-aminosulfonyl, mono- or di(benzyl)aminosulfonyl, polyhaloC₁₋₆alkylsulfonyl, C₁₋₆alkylsulfinyl, phenylC₁₋₄alkylsulfonyl, piperazinylsulfonyl, aminopiperidinylsulfonyl, piperidinylaminosulfonyl, *N*-C₁₋₄alkyl-*N*-piperidinylaminosulfonyl or mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkylsulfonyl;

each R^7 and each R^8 are independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, arylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het², Het⁴ and R^6 ;

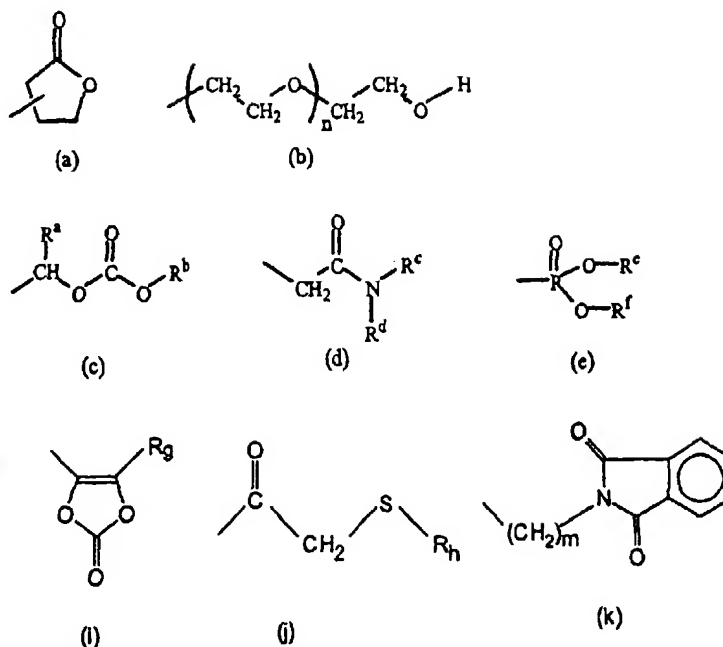
R^9 and R^{10} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, Het³carbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , Het³, Het⁴ and R^6 ;

each R^{11} independently being selected from hydroxy, mercapto, cyano, nitro, halo, trihalomethyl, C_{1-4} alkyloxy optionally substituted with C(=O)-Z- R^{14} , formyl, trihalo C_{1-4} alkylsulfonyloxy, R^6 , NR^7R^8 , C(=O) $NR^{15}R^{16}$, -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} , aryl, aryloxy, arylcarbonyl, C_{3-7} cycloalkyl optionally substituted with C(=O)-Z- R^{14} , C_{3-7} cycloalkyloxy optionally substituted with C(=O)-Z- R^{14} , phthalimide-2-yl, Het³ and C(=O)Het³;

R^{12} and R^{13} are each independently selected from hydrogen, C_{1-4} alkyl, hydroxy C_{1-4} alkyl, dihydroxy C_{1-4} alkyl, phenyl, phenyl C_{1-4} alkyl, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkylcarbonyl, phenylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, phenylaminocarbonyl, phenylaminothiocarbonyl, C_{3-7} cycloalkyl, pyridinyl C_{1-4} alkyl, C_{1-4} alkanediyl-C(=O)-Z- R^{14} , -C(=O)-Z- R^{14} , -Y- C_{1-4} alkanediyl-C(=O)-Z- R^{14} and R^6 ;

each R^{14} independently represents C_{1-4} alkyl substituted with one or more substituents selected from phenyl, di- C_{1-4} alkylamino, cyano, Het¹ and C_{3-7} cycloalkyl, hydrogen, C_{1-20} acyl (having a straight or branched, saturated or unsaturated hydrocarbon chain having 1 to 20 carbon atoms), C_{1-20} alkyl, C_{3-7} cycloalkyl, polyhalo C_{1-20} alkyl or a radical of formula

3



wherein n is 0 to 5 and m is 1 to 4;

R^a , R^b , R^c , R^d , R^e and R^f are each independently hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl; or

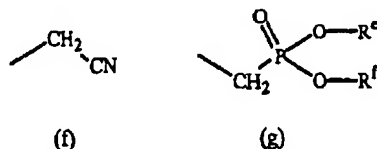
R^e and R^f taken together may form $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$;

R_g and R_h are each independently C_{1-4} alkyl;

each Z independently represents O, S, NH, $-\text{CH}_2-\text{O}-$ or $-\text{CH}_2-\text{S}-$ whereby $-\text{CH}_2-$ is

10 attached to the carbonyl group;

$-\text{Z}-\text{R}^{14}$ taken together form a radical of formula



R^{15} and R^{16} are each independently selected from dihydroxy C_{1-4} alkyl, aryl, aryl C_{1-4} alkyl,

C_{1-4} alkyloxy C_{1-4} alkyl, $-\text{C(=O)-Z-R}^{14}$, arylcarbonyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl,

15 arylaminocarbonyl, arylaminothiocarbonyl, Het³aminocarbonyl, Het³aminothiocarbonyl, pyridinyl C_{1-4} alkyl, Het³, Het⁴ or R^6 ;

aminocarbonylmethylene or mono- or di(C_{1-4} alkyl)aminocarbonylmethylene;

aryl represents phenyl optionally substituted with one, two or three substituents each

independently selected from nitro, azido, cyano, halo, hydroxy, C_{1-4} alkyl, C_{3-7} cyclo-

alkyl, C₁₋₄alkyloxy, formyl, polyhaloC₁₋₄alkyl, NR⁹R¹⁰, C(=O)NR⁹R¹⁰, C(=O)-Z-R¹⁴, R⁶, -O-R⁶, phenyl, Het³, C(=O)Het³ and C₁₋₄alkyl substituted with one or more substituents each independently selected from halo, hydroxy, C₁₋₄alkyloxy, C(=O)-Z-R¹⁴, -Y-C₁₋₄alkanediy-C(=O)-Z-R¹⁴, Het³ or NR⁹R¹⁰;

- 5 Het¹ represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-
10 d]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolyl, phtalazinyl, quinazolyl, quinoxalyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]-thiazolyl; wherein said heterocycles each independently may optionally be substituted
15 with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het² and R¹¹;

Het² represents a heterocycle selected from pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, triazolyl, tetrazolyl, furanyl, tetrahydrofuranyl, thienyl, thiolanyl, dioxolanyl, oxazolyl, oxazolinyl, isoxazolyl, thiazolyl, thiazolinyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl, dioxanyl, dithianyl, trithianyl, triazinyl, benzothienyl, isobenzothienyl, benzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxazolyl, indolyl, isoindolyl, indolinyl, purinyl, 1*H*-pyrazolo[3,4-*d*]pyrimidinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolyl, phtalazinyl, quinazolyl, quinoxalyl, thiazolopyridinyl, oxazolopyridinyl and imidazo[2,1-*b*]thiazolyl; wherein said heterocycles each independently may optionally
20 be substituted with one, or where possible, two or three substituents each independently selected from Het⁴, R¹¹ and C₁₋₄alkyl optionally substituted with one or two substituents independently selected from Het⁴ and R¹¹;

- 25
30 Het³ represents a monocyclic heterocycle selected from pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl and tetrahydropyranyl; wherein said monocyclic heterocycles each independently may optionally be substituted with, where possible, one, two, three or four substituents each independently selected from hydroxy, C₁₋₄alkyl,

C_{1-4} alkyloxy, C_{1-4} alkylcarbonyl, piperidinyl, $NR^{12}R^{13}$, $C(=O)-Z-R^{14}$, R^6 and C_{1-4} alkyl substituted with one or two substituents independently selected from hydroxy,

C_{1-4} alkyloxy, phenyl, $C(=O)-Z-R^{14}$, $-Y-C_{1-4}$ alkanediyl- $C(=O)-Z-R^{14}$, R^6 and $NR^{12}R^{13}$;

Het⁴ represents a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl,

- 5 triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl provided however that

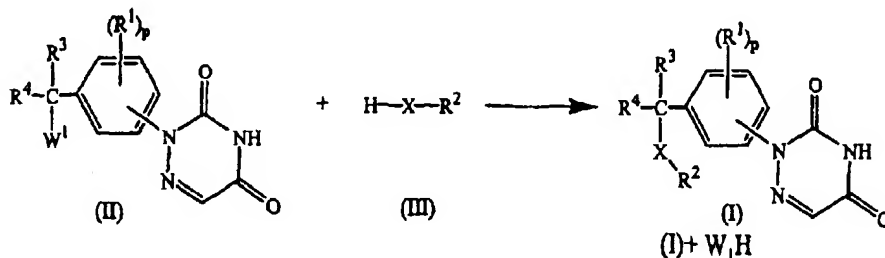
- R^2 is other than C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, aminocarbonyl; and
- R^7 , R^8 , R^9 and R^{10} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkyloxycarbonylcarbonyl $C(=O)-O-R^{14}$, C_{1-4} alkanediyl $C(=O)-O-R^{14}$ and $-Y-C_{1-4}$ alkanediyl $C(=O)-O-R^{14}$; and
- R^{12} and R^{13} are other than C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl, C_{1-4} alkylcarbonylcarbonyl; and
- R^{11} is other than $C(=O)-O-R^{14}$, $Y-C_{1-4}$ alkanediyl - $C(=O)-OR^{14}$, $C(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl or $C(=O)NHC_{3-7}$ cycloalkyl; and
- R^{14} is other than hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl, aminocarbonylmethylene, mono- or di (C_{1-4} alkyl) aminocarbonylmethylene in the event Z is O; and
- R^{15} and R^{16} are other than aminocarbonyl, C_{1-4} alkylcarbonyloxy- C_{1-4} alkylcarbonyl, hydroxy C_{1-4} alkylcarbonyl or C_{1-4} alkyloxycarbonylcarbonyl; and
- 20 • Aryl is other than phenyl substituted with $C(=O)-O-R^{14}$, $C(=O)NH_2$, $C(=O)NHC_{1-4}$ alkyl, $C(=O)NHC_{3-7}$ cycloalkyl and/or with C_{1-4} alkyl substituted with $C(=O)-O-R^{14}$ or $Y-C_{1-4}$ alkanediyl - $C(=O)-O-R^{14}$; and
- Het³ is other than a monocyclic heterocycle substituted with $C(=O)-O-R^{14}$ and/or with C_{1-4} alkyl substituted with $C(=O)-O-R^{14}$ and/or $Y-C_{1-4}$ alkanediyl - $C(=O)-O-R^{14}$; and
- 25 • The said compound of formula (I) contains at least one - $C(=O)-Z-R^{14}$ moiety.

2. A compound as claimed in claim 1 wherein the 6-azauracil moiety is in the para position relative to the carbon atom bearing the -X- R^2 , R^3 and R^4 substituents.

- 30 3. A compound as claimed in claims 1 or 2 wherein R^2 is a monocyclic heterocycle selected from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyranyl, pyridazinyl and triazinyl, wherein said monocyclic

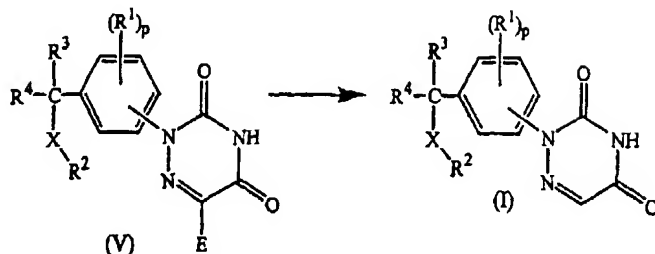
heterocycles each independently may optionally be substituted with one, or where possible, two or three substituents each independently selected from Het², R¹¹ and C₁₋₄alkyl optionally substituted with Het² or R¹¹.

- 5 4. A compound as claimed in any one of claims 1 to 3 wherein R³ and R⁴ are both methyl and -X-R² is Het¹.
5. A compound as claimed in any one of claims 1 to 4 wherein p is 1 or 2 and each R¹ is chloro.
- 10 6. A composition comprising a pharmaceutically acceptable carrier and, as active ingredient, a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.
- 15 7. A process for preparing a composition as claimed in claim 6, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 5.
8. A compound as claimed in any one of claims 1 to 5 for use as a medicine.
- 20 9. Use of a compound as claimed in any one of claims 1 to 5 in the manufacture of a medicament for treating eosinophil-dependent inflammatory diseases.
10. A process for preparing a compound as claimed in claim 1, characterized by,
- 25 a) reacting an intermediate of formula (II) wherein W¹ is a suitable leaving group with an appropriate reagent of formula (III) optionally in a reaction-inert solvent and optionally in the presence of a base at a temperature ranging between - 70°C and reflux temperature;



wherein R^1 , R^2 , R^3 , R^4 , p and X are as defined in claim 1 or;

b) eliminating the group E of a triazinedione of formula (V)



wherein E is an appropriate electron attracting group and R^1 , R^2 , R^4 , X and p are as defined in claim 1;

and, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and also, if desired, preparing stereochemically isomeric forms or *N*-oxide forms thereof.

11. A process of marking a receptor comprising the steps of

- a) radiolabelling a compound as defined in claim 1;
- b) administering said radiolabelled compound to biological material,
- c) detecting the emissions from the radiolabelled compound.

12. A process of imaging an organ, characterized by, administering a sufficient

amount of a radiolabelled compound of formula (I) in an appropriate composition, and detecting the emissions from the radioactive compound.

BIBLIOGRAPHIC DATA OF APPLICATION: 99870170.0 (= EP application)

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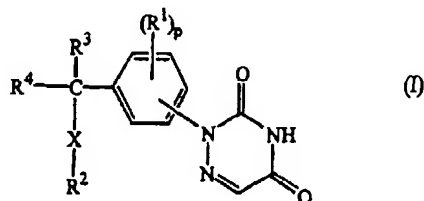
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ABSTRACTNON-STEROIDAL IL-5 INHIBITORS, PROCESSES FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

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The present invention is concerned with the compounds of formula



- the *N*-oxides, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein *p* is 0 to 4; *X* is O, S, NR⁵ or a direct bond; *Y* is O, S, NR⁵ or S(O)₂; R¹ independently is C(=O)-Z-R¹⁴, C₁₋₆alkyl, halo, polyhaloC₁₋₆alkyl, hydroxy, mercapto, C₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkylcarbonyloxy, aryl, cyano, nitro, Het³, NR⁷R⁸ or substituted C₁₋₄alkyl; R² is Het¹, C₃₋₇cycloalkyl or optionally substituted C₁₋₆alkyl and if *X* is O, S or NR⁵, then R² may also represent C(=O)-Z-R¹⁴, aminothiocarbonyl, C₁₋₄alkylcarbonyl, C₁₋₄alkylthiocarbonyl, arylcarbonyl, arylthiocarbonyl, Het¹carbonyl or Het¹thiocarbonyl; R³ and R⁴ independently are hydrogen, C₁₋₆alkyl or C₃₋₇cycloalkyl or R³ and R⁴ together form a C₂₋₆alkanediyl; R⁵ is hydrogen or C₁₋₄alkyl; R⁷ and R⁸ are independently hydrogen, optionally substituted C₁₋₄alkyl, aryl, a carbonyl containing moiety, C₃₋₇cycloalkyl, -Y-C₁₋₄alkanediyl-C(=O)-Z-R¹⁴ or Het³; R¹⁴ is hydrogen, C₁₋₂₀alkyl, C₃₋₇cycloalkyl, C₁₋₂₀acyl or another radical; Z is O, S, NH, -CH₂O- or -CH₂S- whereby -CH₂- is attached to the carbonyl group; aryl is optionally substituted phenyl; Het¹, Het², Het³ and Het⁴ are optionally substituted heterocycles, provided that the said compounds contain at least one -C(=O)-Z-R₁₄ moiety; to processes for their preparation and pharmaceutical compositions comprising them. It further relates to their use as a medicine.

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